SUMMARY OF SAFETY AND EFFECTIVENESS DATA FOR A SUPPLEMENTAL PREMARKET APPLICATION

I. GENERAL INFORMATION

Device Generic Name: balafilcon A hydrophilic contact lens

Device Trade Name: PureVision™ Visibility Tinted Contact Lens

Applicant's Name and Address: Bausch & Lomb Incorporated
1400 N. Goodman Street
P.O. Box 450
Rochester, NY 14603-0450

Date of Panel Recommendation: None

Premarket Approval (PMA) Application Number: P980006/S004

Date of Notice of Approval to Applicant: November 20, 2001

The BAUSCH & LOMB® PureVision™ (balafilcon A) Visibility Tinted Contact Lens was approved on February 5, 1999 under P980006 for the indication of daily wear or extended wear from 1 to 7 days between removals, for cleaning and disinfection or disposal of the lens, as recommended for the eyecare proctitioner. The lens was indicated for the correction of refractive ametropia (myopia and hyperopia) in aphakic and/or not-aphakic persons with non-diseased eyes, exhibiting astigmatism of 2.00 diopters or less, that does not interfere with visual acuity.

The sponsor submitted the current supplement to further expand the indication statement. The updated clinical data to support this expanded indication are provided in this summary. The preclinical test results were presented in the original PMA application. For more information on the data that supported the approved indication, the summary of safety and effectiveness data (SSED) for P980006 should be referenced. Written requests for copies of the SSED can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20857. The summary can also be found on the FDA CDRH Internet Home Page located at http://www.fda.gov/cdrh/pmapage.html.

II. INDICATIONS FOR USE

The BAUSCH & LOMB® PureVision™ (balafilcon A) Visibility Tinted Contact Lens is indicated for daily wear or extended wear from 1 to 30 days between removals, for cleaning and disinfection or disposal of the lens, as recommended by the eye care

and hyperopia) in aphakic and/or not-aphakic persons with non-diseased eyes, exhibiting astigmatism of 2.00 diopters or less, that does not interfere with visual acuity. The lens may be prescribed for Frequent/Planned Replacement Wear or Disposable Wear in spherical powers ranging from +8.00D to –20.00D when prescribed for up to 30 days of extended wear and from +20.00D to –20.00D for daily wear or extended wear up to 7 days.

III. CONTRAINDICATIONS

- Acute and subacute inflammation or infection of the anterior chamber of the eye
- Any eye disease, injury, or abnormality that affects the cornea, conjunctiva, or eyelids
- Severe insufficiency of lacrimal secretion (dry eyes)
- Corneal hypoesthesia (reduced corneal sensitivity)
- Any systemic disease that may affect the eye or be exaggerated by wearing contact lenses
- Allergic reactions of ocular surfaces or adnexa (surrounding tissue) that may be induced or exaggerated by wearing contact lenses or use of contact lens solutions
- Allergy to any ingredient, such as mercury or Thimerosal, in a solution which is to be used to care for the PureVision™ Contact Lens
- Any active corneal infection (bacterial, fungal, or viral)
- If eyes become red or irritated

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PureVision™ contact lens labeling (attached).

V. DEVICE DESCRIPTION

The BAUSCH & LOMB® PureVision™ (balafilcon A) Visibility Tinted Contact Lens is a soft hydrophilic contact lens which is available as a spherical lens. The lens material, balafilcon A, is a copolymer of a silicone vinyl carbamate, N-vinyl-pyrrolidone, a siloxane crosslinker and a vinyl alanine wetting monomer, and is 36% water by weight when immersed in a sterile borate buffered saline solution. This lens is tinted blue with up to 300 ppm of Reactive Blue Dye 246.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternate practices and procedures to the BAUSCH & LOMB® PureVision™ (balafilcon A) Visibility Tinted Contact Lens are other daily and extended wear soft contact lenses, daily and extended wear rigid gas permeable extended wear contact lenses, radial keratotomy, photorefractive keratectomy, laser-assisted in situ keratomiluesis (LASIK), and spectacles.

VII. MARKETING HISTORY

The PureVision™ (balafilcon A) Visibility Tinted Contact Lens is commercially available in the United States for daily wear and up to 7 days of extended wear. The PureVision™ lens was introduced outside the U.S. in 1999 and is commercially available in more than 40 countries for up to 30 days of continuous wear. Regulatory approvals for 30 day continuous wear include Poland, the European Union, January, 1999; Australia, March, 1999; and Canada, November, 2000.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects on health associated with extended wear contact lenses include eye problems such as corneal ulcers, epithelial microcysts, infiltrates and endothelial polymegathism. The risk of corneal ulcer has been shown to be greater among users of extended wear contact lenses than among users of daily wear contact lenses. The risk among extended wear users increases with the number of consecutive days that the lenses are worn between removals, beginning with the first overnight use. In addition, smoking increases the risk of corneal ulcers for contact lens users, especially when lenses are worn overnight or while sleeping. Strict compliance with the proper lens care regimen and wearing schedule is essential in minimizing risk.

IX. SUMMARY OF PRECLINICAL STUDIES

No additional preclinical studies were required for the indication of extended wear from 1 to 30 days. Please refer to the SSED of the original PMA, P980006.

X. SUMMARY OF CLINICAL STUDY

A. Study Objective

The objective of this study was to evaluate the safety and efficacy of the PureVision™ Contact Lens worn on a 30-day extended wear basis, compared to a currently marketed hydrophilic (soft) Control contact lens worn on a 7-day extended wear basis. The study, which started in June 1999 and ended in December 2000, was carried out under IDE G980330.

B. Study Design

This was an 820 subject, 12 month, controlled, contralateral, randomized, non-blinded study conducted by 35 investigators. Patients were fitted with a PureVision™ lens on one eye while the contralateral eye was fitted with a conventional Control lens. Randomization tables determined which eye wore which lens. The PureVision™ lens was worn for up to 29 consecutive nights, while the control lens was worn for up to 6 consecutive nights. The test lens was replaced every 30 days, while the control lens was removed, cleaned and disinfected every 7th night and replaced every 14 days. The lens type worn in the right or left eye remained constant throughout the study. Subjects who needed a period to adapt to contact lens wear were placed in daily wear for one week before introduction to overnight wear. Subjects who could not enter extended wear within 1 week were discontinued.

The primary endpoints for safety and efficacy were:

1. grade 2 and higher corneal infiltrates (safety endpoint), and
2. grade 2 and higher slit lamp findings (safety endpoint),
3. contact lens corrected visual acuity worse than 20/40 (efficacy endpoint).

For each key endpoint, the rates (incidents of endpoint/number of eyes) experienced by eyes in the PureVision Contact Lens and Control lenses were calculated. The difference in rates between the two lens types was determined and a 95% confidence interval for the difference was calculated. For each key endpoint, a "clinically significant difference" in the rates was established before the study started. These "clinically significant differences" were as follows: 10% for total slit lamp findings ≥ Grade 2, 5% for corneal infiltrates ≥ Grade 2, and 5% for the acuity endpoint. For example, if the true rates of endpoint infiltrates in the subject population were 9.99% in the PureVision Contact Lens and 5% in the Control lens, these rates would be considered substantially equivalent (difference <5%).

In order to be successful for a given endpoint, the upper 95% confidence limit for the difference in the study rates had to be less than the pre-established "clinically significant difference." This means that we are 95% confident that the true difference is within tolerance.

The statistical analyses utilized the study data pooled over the investigative sites. The patient bases from the sites were similar with respect to size and demographics. All investigative sites followed the same detailed investigative plan.

C. Subject Assessments

After being placed into extended wear, all subjects were scheduled follow-up visits at 24 hours, 10 days, 1 month, 2 months, 3, 6, 9, and 12 months. Investigators

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evaluated lenses for fitting performance, lens surface characteristics, and physiological response. Patients were asked to complete Patient Assessment Forms at all scheduled and unscheduled visits. Patients were also required to complete a Weekly Patient Diary at home.

At the initial visit, demographic information was collected and examination determined the refraction, visual acuity (VA), keratometry readings, and slit-lamp findings.

At each follow-up visit, the investigator did the following:

- Obtained average wearing time and had the patient complete the Patient Assessment Forms (rating of symptoms);
- Evaluated lenses on eye (with slit-lamp); determined lens VA, over-refraction, lens deposits and wettability;
- Complete slit-lamp evaluation;
- Reviewed patients Weekly Patient Diary;
- Reviewed patient's Lens Replacement Log to ensure compliance.

The Patient Assessment Form was used to enable the patient to report the presence or absence of burning/stinging, discomfort, dryness, variable vision, blurred vision, redness, tearing, excess secretions, and lens handling difficulty. At each follow-up visit, patients were asked to complete a Patient Assessment Form. If present, each symptom/complaint was rated on an analog scale. This was later converted to a digital scale, with 0 being best case and 100 being worst case.

At the final visit, the investigator also obtained a refraction with VA and keratometry readings, and compared these to those obtained at the initial visit (with explanations for differences).

D. Demographic Data

Study subjects included adapted and unadapted contact lens wearers. There were no restrictions as to the patient's gender or occupation, but patients were required to be of legal age (typically 18 or 21) and have the legal capacity to volunteer. The ages of the patients ranged from 18 to 74 years, with a mean age of 33.6, and included 574 females and 228 males, with a ratio of 2.52 females to every male.

The previous lens wearing experience of the patients that participated in the study was 5% no lens wear, 43% daily wear, and 51% extended wear. The refractive errors of the patients ranged from –0.25 to –11.75D, and included up to –2.00D of astigmatism. The lens power ranges used were –0.5 to –9.0D for the PureVision™ lens and –0.5 to-8.5D for the Control lens.

E. Data Analysis and Results

The safety and efficacy goals were met for all three key endpoints. Results are as follows:

Endpoint	PureVision		Control		Relative Risk PureVision/ Control	Difference in %	Upper 95% Confidence Level	Clinically Significant Difference
	n	%	n	%				
Slit Lamp Findings ≥ Grade 2	138	17.5%	139	7.6%	1.0	-0.1%	2.6%	10.0%
Corneal Infiltrates ≥ Grade 2	23	2.9%	10	1.3%	2.3	1.6%	2.9%	5.0%
Visual Acuity Worse than 20/40	0	0.0%	2	0.3%	0.0	-0.3%	0.1%	5.0%

Summary of Slit Lamp Findings

Slit lamp examinations were conducted at every study visit. Each graded slit lamp parameter was scored on a qualitative grade scale ranging from 0 to 4, with Grade 0 representing the absence of findings, and Grades 1 through 4 representing successively worse findings. For each study eye, a determination was made for each parameter as to whether, or not a positive finding was presented at any visit. The following table describes slit lamp findings ≥ Grade 2 and ungraded slit lamp findings.

	PureVision	**Control**
Graded Slit Lamp Findings (≥ Grade 2)		
Any Finding[1,2]	**17.5%**	**17.6%**
Corneal Staining	8.2%	8.4%
Limbal Injection	3.7%	4.3%
Bulbar Injection	5.2%	4.7%
Tarsal Conjunctival Abnormalities	3.9%	3.9%
Corneal Infiltrates[1]	**2.9%**	**1.3%**
Epithelial Edema	1.3%	1.4%
Epithelial Microcysts	1.0%	1.0%
Corneal Neovascularization	1.0%	1.7%

Ungraded Slit Lamp Findings		
Other Anterior Segment Abnormalities[3]	13.2%	13.8%
External Adnexa Abnormalities	2.7%	2.7%
Conjunctivitis	2.4%	2.0%
Corneal Striae	0.0%	0.3%

1/ Slit Lamp Finding and Corneal Infiltrates ≥ Grade 2 were the safety endpoints for this study.

2/ The total of all Graded slit lamp findings does not equal the category of Any Finding.

3/ The more common findings identified as Other Anterior Segment Abnormalities included: conjunctival staining; dimple veils; mucin balls; lipid deposits; and ghost vessels.

It should be noted that the PureVision Contact Lens and the Control lens were each fit on only the right or left eye for each subject. Rates per subject are expected to be higher when lenses are fit on both eyes.

Corneal Infiltrates

The following table describes the rate of corneal infiltrates according to the lens power used. In this study, as PureVision lens power increased, the rate of corneal infiltrates increased. Due to a limited number of lenses in the high power range, definitive statistical conclusions cannot be drawn. However, the overall (total) rate of corneal infiltrates was found to be equivalent to the Control lens within the defined clinically significant difference of 5%.

	Lens Power	**Corneal Infiltrates (≥ Grade 2)**
PureVision	Plano to –3.00	1.7%
	-3.25 to –6.00	3.2%
	>-6.00	6.4%
	Total	2.9%
Control	Plano to –3.00	0.9%
	-3.25 to –6.00	1.5%
	>-6.00	1.3%
	Total	1.3%

Other Lens-Related Adverse Events

In addition to the outcomes described above, the following lens related adverse events were noted. This table does not include conjunctivitis or tarsal conjunctival abnormalities, e.g., giant papillary conjunctivitis.

Other Important Lens-Related Adverse Events

	PureVision	Control
Corneal Scar	14 (1.8%)	5 (0.6%)
Other Ocular Inflammation*	10 (1.3%)	2 (0.3%)
Anterior Chamber Reaction	2 (0.3%)	1 (0.1%)
Permanent Loss of Vision	0 (0.0%)	0 (0.0%)

* Other Ocular Inflammation includes episcleritis, scleritis, iritis/uveitis. This condition was reported in association with other conditions such as keratitis, corneal infiltrates, blepharitis, corneal abrasion, and contact lens over wear.

It should be noted that the PureVision Contact Lens and Control lenses were each fit on only the right or left eye for each subject. Rates per subject are expected to be higher when lenses are fit on both eyes.

Visual Acuity

The contact lens visual acuity was measured at each scheduled and unscheduled follow-up visit throughout the one-year study. For the 610 subjects that completed the study, visual acuity of 20/20 or better was reported for 87% and 86% of the measurements for the PureVision Contact Lens and Control lens, respectively. Similarly, visual acuity of 20/25 or better was reported 98% and 97% of the times for the PureVision Contact Lens and Control lens.

Wearing Time

In this U.S. clinical study subjects were required to maintain a minimum wearing time in order to continue in the study. For the subjects that completed the study, the average continuous wear time for the PureVision Contact Lens was at least 28.0 days per month, from the 2-Month visit through the 12-Month visit. At these visits the same subjects reported they were able to wear the PureVision Contact Lens at least 22 days continuously 94% of the times they were asked.

During the course of the study, 15 subjects were discontinued from the study because they were not able to wear the PureVision Contact Lens for 30 days. Twenty-one (21) subjects were discontinued from the study because they were not able to wear the Control lens for 7 days.

Discontinued Subjects

Of the 820 subjects enrolled, 610 completed the 12 month clinical study. Ten subjects discontinued in the daily wear adaptation period, 182 discontinued during extended wear, 18 subjects were not dispensed lenses. The following table includes the reasons for discontinuation:

Non Clnical Reasons	PureVision #	PureVision %	Control #	Control %
Pt Instructions	8	4.4	9	5.0
Lost to Follow-Up	31	17.0	31	17.0
Missed Visits	5	2.8	5	2.8
Other Eye Discontinued	28	15.4	15	8.2
Switched Lens	2	1.1	1	0.6
Other	36	19.8	36	19.8
Motivation	18	10.0	17	9.3
Total	128	70.3	11	62.6
Clinical Reasons				
Adverse Effect	3	1.7	1	0.6
Positive Slit Lamp Findings	10	5.5	9	5.0
Study Related Signs/Symptoms	24	13.2	29	15.9
Unacceptable VA	2	1.1	3	1.7
Centration	0	0.0	3	1.7
Movement	0	0.0	1	0.6
Wearing Schedule	15	8.2	21	11.5
Other (Discomfort)	0	0.0	1	0.6
Total	54	29.7	68	37.4

Patient Symptoms and Complaints

Patients were asked to report study related symptoms and complaints at each follow-up visit. The following table summarizes the rates:

	Overall Occurrence n	Test Lens	Control Lens	Lower Confidence Limit for Difference(%)	Upper Confidence Limit for Difference(%)
Any Symptom	792	84.85%	86.36%	-3.7	0.7
Burning/Stinging	789	42.08%	41.83%	-2.6	3.1
Discomfort	789	58.56%	61.09%	-5.9	0.9
Dryness	789	72.37%	75.29%	-5.2	-0.6
Variable Vision	789	28.52%	30.54%	-4.7	0.6
Blurred Vision	789	39.04%	41.32%	-5.3	0.7
Redness	789	40.94%	41.83%	-3.9	2.1
Excess Tearing	789	21.04%	21.80%	-3.5	2
Excess Secretions	789	25.98%	23.83%	-0.5	4.8
Handling	789	12.55%	32.83%	-23.4	-16.9

If present, each symptom was rated on an analog scale. This was later converted to a digital scale, with 0 being best case and 100 being worst case. Differences in ratings were minor, with the Test lens generally receiving slightly more favorable scores. For each patient the difference in the rating was determined, and a 2-sided 95% confidence interval of the difference was calculated. Equivalence was demonstrated when the interval was entirely between ±10. In a comparison of the magnitude/severity of symptoms, the two lenses were found equivalent for all categories at all visits and overall.

Visual Acuity Line Changes

Investigators were asked to note and explain every instance in which the lens VA showed a decrease of 2 or more lines from baseline best corrected spectacle VA. Only 1.7% of PureVision™ eyes and 1.8% of Control eyes showed lens VA decreases of 2 or more lines throughout the study. Using ±10% as the tolerance for equivalence it is concluded that at all visits and overall the PureVision™ and Control lenses were equivalent with respect to lens VA and lens VA changes.

Keratometry and Mire Reflex

Keratometry changes from initial to final visit were evaluated. There were 28 reported changes of more than 1 diopter in corneal curvature (18 PureVision™, 10 Control). Although the mean changes for PureVision™ eyes in both meridians (-0.12 H, -0.18 V) and the horizontal changes for Control eyes were statistically significant, all mean changes were less than 0.25D.

Almost 99% of completed eyes had clear and undistorted keratometry mire reflexes. Nineteen completed eyes (10 PureVision™, 9 Control) were reported as slightly distorted at the diagnostic fit visit. Nine completed eyes (3 PureVision™ and 6 Control) were reported as slightly distorted at the final visit.

Refractive Changes

There were 2 completed Control eyes and 8 completed PureVision™ eyes with a refractive change of more than one diopter from the baseline reading to the final visit. Mean refractive change in the PureVision™ group was +0.07D and mean change in the Control group was –0.12D

Lens Replacements

There were 168 unscheduled replacements for the PureVision™ lens and 149 unscheduled replacements for the Control lens. Of the 317 total unscheduled lens replacements, the main reasons were to provide extra/backup lenses and changed power.

Lens Centration and Movement

Lens centration was scored as excellent, good, fair, or poor at each visit. Lens movement was similarly rated as adequate, excessive, insufficient, or adherence. Lens centration was described as good or excellent at 99.6% of study visits for the PureVision™ lens and at 96.5% for the Control lens. Lens movement was described as adequate at more than 96% of the study visits for both the PureVision™ and Control lenses. Adherence was reported at only 1 visit for the PureVision™ lens, and at only 3 visits for the Control lens.

Data were analyzed in the following manner. If centration were not classified as excellent, it was considered to be sub-optimal at a given visit. If movement were not classified as adequate, it was considered to be sub-optimal. For both parameters, the frequency of "sub-optimal' findings was calculated for each time interval and a confidence interval was calculated for the difference in the frequency. To support a finding of equivalence, the confidence interval would have to be entirely between ±10%. Based on this analysis, it can be concluded that the PureVision™ lens and the Control lens were equivalent with regard to lens movement and that the PureVision™ lens was better with respect to lens centration.

Lens Deposits, Lens Debris and Lens Wettability

At each visit, lens deposits, debris, and wettability were rated on a scale from 0 to 4. The ratings for the two lenses were generally very comparable.

For these parameters, each eye was categorized as to whether or not a sub-optimal score was present at any point during each time frame. For each parameter a 95% confidence interval was calculated for the difference in the occurrence rate of "sub-optimal" findings. In order to support a conclusion of equivalence, the confidence interval had to lie entirely between ±10%. Based on this analysis it can be concluded that the PureVision™ lens and the Control lens were equivalent with regard to lens deposits, lens debris and lens wettability.

Patient Diaries

Patients were asked to complete a Weekly Patient Diary once each week describing their contact lens wearing experience. This included lens replacement information, lens wearing time, and the presence or absence of symptoms and complaints. The information collected concerning symptoms was similar to that collected on the Patient Assessment Forms. For each time frame (after 3, 6, 9, and 12 months), a sub-optimal report for a diary symptom parameter was defined as the indication of symptom presence on over 20 % of the forms submitted during the time frame.

For these overlapping time frames, for each parameter, analyses were performed to compare the rates of occurrence of "sub-optimal findings." Each comparison was based on the 95% confidence interval for the difference between the occurrence rates. A conclusion of equivalence was supported by a confidence interval entirely lying between ±10%. Based on this analysis it can be concluded that the PureVision™ lens and the Control lens were equivalent with regard to patient diary symptoms and complaints. The diary findings largely confirm the findings reported in other sections, concerning patient symptoms, lens replacements, and lens wearing time.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

The data in this application support reasonable assurance of the safety and effectiveness of the PureVision™ lens when used in accordance with the approved indications for use. Although the potential exists for minor differences in physiological response by gender for the target population, minimal number of clinically significant findings does not indicate that gender differences are of clinical importance for this device.

XII. PANEL RECOMMENDATION

The Ophthalmic Devices Panel, an FDA advisory committee previously reviewed a PMA application for a contact lens indicated for extended wear up to 30 days. Although this PMA supplement was the second-of-a kind, it was originally scheduled for discussion before the Ophthalmic Devices Panel on September 21, 2001 to discuss the need for a post market study and to provide the Panel the opportunity to review clinical data from a contralateral eye clinical study. Two primary Panel reviewers had completed their reviews in preparation for the meeting.

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Due to the tragic events on September 11, 2001, the September 21, 2001 Panel meeting was cancelled. During subsequent discussion, it was decided that primary clinical issues in the PMA substantially duplicated information previously reviewed by this panel. Additional homework assignments from two additional Panel members were obtained to corroborate the recommendations of the two primary reviewers in lieu of a full Panel discussion.

The four advisory panel reviewers recommended that P980006/S004 for the PureVision™ Visibility Tinted Contact Lens for extended wear from 1 to 30 days between removals be approved, subject to a post approval study to assess the long term rates of microbial keratitis and associated loss of vision.

Therefore, in accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the full Ophthalmic Devices Panel, for review at an advisory panel meeting.

XIII. FDA DECISION

CDRH issued an approval order on November 20, 2001

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the attached labeling.

Hazards to Health from Use of the Device: See the Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order